Therapeutic Class Review
Glycopeptides

Overview/Summary

Vancomycin, a tricyclic glycopepetide, is a bactericidal antibiotic that binds to the bacterial cell wall causing immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane.[1,2] Vancomycin is used parenterally and orally, where only the injectable formulation is available generically. Vancomycin capsules are used in the treatment of enterocolitis due to *Staphylococcus aureus* (including methicillin-resistant strains) or antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*.[2] Oral vancomycin has been shown to be effective for antibiotic-associated pseudomembranous colitis caused by *C difficile* in clinical trials demonstrating similar efficacy with other treatment options including metronidazole.[3-5] Current guidelines recommended metronidazole for mild to moderate infections and oral vancomycin for severe infections.[6] Vancomycin injection, on the other hand, has broad activity against most gram-positive bacteria; however, it is not generally effective for gram-negative organisms. It is indicated for serious infections caused by susceptible strains of methicillin-resistant staphylococci, as well as other infections caused by staphylococci including endocarditis, septicemia, bone infections, lower respiratory tract infections, and skin and skin structure infections. Vancomycin injection also has reported efficacy alone or as adjunct treatment for endocarditis caused by viridans group streptococci, *Streptococcus bovis*, or diphtheroids (coryneform bacteria).[1]

This therapeutic class review focuses on the oral formulation of vancomycin.

Medications

Table 1. Medications Included Within Class Review

Generic Name	Medication Class	Generic Availability
Vancomycin (Vancocin®)	Glycopeptides	-

Vancomycin has been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration-approved indications for vancomycin that are noted in Table 3. Vancomycin may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible Vancomycin[2]

Bacteria	Vancomycin
Clostridium difficile	✔ *
Staphylococcus aureus (methicillin-susceptible)	✔ †
Staphylococcus aureus (methicillin-resistant)	✔ †

*Antibiotic-associated pseudomembranous colitis.
†Associated with enterocolitis.

Indications

Table 3. Food and Drug Administration (FDA) Approved Indications[2]

Indication	Vancomycin
Enterocolitis caused by *Staphylococcus aureus* (methicillin- susceptible and -resistant strains)	✔
Antibiotic-associated pseudomembranous colitis caused by *C difficile*	✔

Pharmacokinetics

Table 4. Pharmacokinetics[1,2]

Generic Name	Bioavailability (%)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Half-Life (hours)
Vancomycin	<5	Not reported	0.76	No	4 to 6

Clinical Trials

Table 4 includes clinical trials for the Food and Drug Administration (FDA)-approved indication for vancomycin.

For the treatment of pseudomembranous colitis caused by *Clostridium difficile* infection, Zar et al compared oral vancomycin to oral metronidazole in a double-blind, randomized trial and stratified the results by severity of disease. For mild disease there was no significant differences in cure rate between metronidazole and vancomycin (*P*=0.36). However, the cure rate in severe disease was significantly higher with vancomycin (*P*=0.02). There was no significant difference between the treatments in relapse rates.[3]

Louie et al conducted a randomized, double-blind trial in which a noninferiority design was utilized to demonstrate the efficacy of fidaxomicin compared to vancomycin in adult patients with *C difficile*-associated diarrhea. The rates of clinical cure (resolution of symptoms and no need for further therapy for *C difficile* infection as of the second day after the end of the course of therapy) with fidaxomicin were noninferior to those achieved with vancomycin (88.2 vs 85.8%). For the secondary endpoints, fidaxomicin had a significantly lower recurrence of infection (reappearance of more than three diarrheal stools per 24 hour period within four weeks after cessation of therapy; *C difficile* toxin A, B or both in stool and a need for retreatment for *C difficile* infection) (15.4 vs 25.3%; 95% confidence interval [CI], -16.6 to -2.9; *P*=0.005) and a significantly higher global cure (resolution of diarrhea without recurrence) (74.6 vs 64.1%; 95% CI, 3.1 to 17.7; *P*=0.006).[4]

A meta-analysis comparing vancomycin to other treatments for pseudomembranous colitis cause by *C difficile* infection found no difference between metronidazole and vancomycin in any of the primary endpoints including symptomatic resolution and cure and bacteriologic resolution and cure.[5]

Table 5. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pseudomembranous Colitis				
Zar et al[3] Vancomycin 125 mg PO QID vs metronidazole 250 mg PO QID	DB, PC, PRO, RCT Patients with diarrhea and *C difficile* toxin A demonstrated in the stool 48 hours after study entry or pseudo-membranous colitis found on endoscopic exam	N=150 21 days	Primary: Cure, treatment failure and relapse Secondary: Not reported	Primary: The cure rate was significantly higher with vancomycin compared to metronidazole (97 vs 84%; *P*=0.006). In patients with mild disease, there was no significant difference in cure rate between vancomycin and metronidazole (98 vs 90%; *P*=0.36). In patients with severe disease, vancomycin had a significantly higher cure rate compared to metronidazole (97 vs 76%; *P*=0.02). There were no significant differences in relapse rate between vancomycin and metronidazole (*P*=0.27) and between mild and severe disease (*P*=0.15). Metronidazole treatment failure was significantly higher in patients with low albumin level (*P*=0.001), with pseudomembranous colitis (*P*=0.001) and hospitalized in the intensive care unit (*P*=0.01). Each treatment group had one patient discontinue due to adverse events. Secondary: Not reported
Louie et al[4] Vancomycin 125 mg PO QID vs fidaxomicin 200 mg PO BID Patients could have received up to four doses of metronidazole or vancomycin in the 24	DB, MC, PG, PRO, RCT Patients ≥16 years of age with a diagnosis of *C difficile* infection (presence of diarrhea and *C difficile* toxin A, B or both in a stool specimen obtained within 48 hours before	N=629 10 days	Primary: Clinical cure Secondary: Recurrence of *C difficile* infection, global cure, time to resolution of diarrhea, safety	Primary: Rates of clinical cure (resolution of symptoms and no need for further therapy for *C difficile* infection as of the second day after the end of the course of therapy) with fidaxomicin were noninferior to those with vancomycin (88.2 vs 85.8%; with a lower boundary of the 97.5% CI for the difference in cure rates of -3.1 percentage points). Subgroup analyses of the rates of clinical cure according to the patients' age, inpatient vs outpatient status, prior occurrence, treatment for *C difficile* infection vs no treatment within 24 hours before the start of the trial, no response vs response to previous metronidazole therapy and use vs nonuse of concomitant systemic antimicrobial therapy showed no significant differences between treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
hour period before randomization and no other potentially effective concurrent treatments for *C difficile* infection.	randomization)			Secondary: Significantly fewer fidaxomicin-treated patients had recurrence of infection (reappearance of more than three diarrheal stools per 24 hour period within four weeks after cessation of therapy; *C difficile* toxin A, B or both in stool and a need for retreatment for *C difficile* infection) (15.4 vs 25.3%; 95% CI, -16.6 to -2.9; *P*=0.005). Fidaxomicin resulted in significantly higher rates of global cure (resolution of diarrhea without recurrence) (74.6 vs 64.1%; 95% CI, 3.1 to 17.7; *P*=0.006). The median time to resolution of diarrhea was shorter with fidaxomicin (58 vs 78 hours; *P* value not reported). There were no significant differences between treatments in the rates of adverse events or serious adverse events. The occurrence of any adverse event during the treatment period until seven days after treatment was reported in 62.3 and 60.4% of fidaxomicin- and vancomycin-treated patients (*P* value not reported). Significantly more serious adverse events related to laboratory test results occurred with fidaxomicin-treated patients (4.7 vs 1.2%; *P*=0.01), without an obvious pattern.
Nelson[5] Vancomycin vs metronidazole or bacitracin or fusidic acid* or teicoplanin* or rifaximin or placebo	MA Patients 18 years of age or older with diarrhea and *C difficile* in stool who had received previous antibiotic therapy for an infection other than *C difficile*	N=1,157 Precise duration of therapy not specified	Primary: Initial resolution of diarrhea, initial conversion of stool to *C difficile* cytotoxin and/or stool culture negative, recurrence of diarrhea, recurrence of fecal *C difficile* cytotoxin and/or positive stool culture, patient response to cessation of prior antibiotic therapy	Primary: For initial symptomatic resolution, metronidazole (RR, 0.97; 95% CI, 0.88 to 1.07; *P*=0.56), bacitracin (RR, 0.94; 95% CI, 0.72 to 1.22; *P*=0.62), teicoplanin (RR, 1.07; 95% CI, 0.95 to 1.19; *P*=0.27), fusidic acid (RR, 0.94; 95% CI, 0.83 to 1.08; *P*=0.40), and rifaximin (RR, 0.90; 95% CI, 0.69 to 1.18; *P*=0.46) were as effective as vancomycin. Vancomycin was more effective than placebo (RR, 6.75; 95% CI, 1.03 to 44.08; *P*=0.03) in a small study (N=21). With regards to symptomatic cure, metronidazole (RR, 1.01; 95% CI, 0.87 to 1.18; *P*=0.85), bacitracin (RR, 0.68; 95% CI, 0.41 to 1.11; *P*=0.12) and fusidic acid (RR, 0.85; 95% CI, 0.61 to 1.17; *P*=0.31) were found similar to vancomycin. Teicoplanin was slightly more effective than vancomycin (RR, 1.21; 95% CI, 1.00 to 1.46; *P*=0.055).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: rates of sepsis, emergent surgery (fecal diversion or colectomy) and death	For initial bacteriologic resolution, vancomycin was more effective than placebo (RR, 7.50; 95% CI, 1.16 to 48.43; *P*=0.03); teicoplanin was more effective than vancomycin (RR, 1.43; 95% CI, 1.14 to 1.81; *P*=0.0021); metronidazole (RR, 0.96; 95% CI, 0.70 to 1.30; *P*=0.78), fusidic acid (RR, 0.96; 95% CI, 0.78 to 1.18; *P*=0.68) and rifaximin (RR, 0.90; 95% CI, 0.69 to 1.18; *P*=0.46) were as effective as vancomycin; and bacitracin was less effective than vancomycin (RR, 0.57; 95% CI, 0.57 to 0.94; *P*=0.028). In terms of bacteriologic cure, in comparison with vancomycin, teicoplanin was more effective (RR, 1.82; 95% CI, 1.19 to 2.78; *P*=0.0058), metronidazole was as effective (RR, 0.74; 95% CI, 0.53 to 1.03; *P*=0.072), and fusidic acid was less effective (RR, 0.68; 95% CI, 0.44 to 1.06; *P*=0.085). Patients were retreated in various ways, which made it difficult to compare the antibacterials for efficacy. There were a total of nine deaths, five of which were specified to be due to underlying illness and not related to treatment. Secondary: These end points occurred infrequently in all of the studies.
Endocarditis				
Fowler et al[7] Daptomycin 6 mg/kg IV once daily vs standard therapy: either vancomycin 1 g IV every 12 hours or an antistaphylococcal penicillin depending on susceptibility to	MC, OL, PRO, RCT Patients with *S aureus* bacteremia with or without endocarditis	N=235 Duration of therapy determined by investigator based upon diagnosis	Primary: Clinical success rate in each group of the modified ITT population at 42 days after end of therapy, failure (clinical failure, microbiologic failure, death, failure to obtain blood culture, receipt of potentially effective nonstudy antibiotics, or	Primary: In the modified ITT population, successful outcome was noted in 53/120 patients in the daptomycin group (44.2%) vs 48/115 patients in the standard-therapy group (41.7%). Directly following the end of therapy, success rates were 61.7% and 60.9% in the daptomycin and standard therapy groups, respectively. The baseline pathogen was determined to be MRSA in 37.5 and 38.3% of patients in the daptomycin and standard therapy groups, respectively. In the daptomycin group, patients were diagnosed with uncomplicated bacteremia (26.7%), complicated bacteremia (50.0%), uncomplicated

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methicillin (nafcillin, oxacillin, flucloxacillin*) 2 g every 4 hours			premature discontinuation) Secondary: Not reported	right-sided endocarditis (5.0%), complicated right-sided endocarditis (10.8%), or left-sided endocarditis (7.5%). In the standard therapy group, patients were diagnosed with uncomplicated bacteremia (25.2%), complicated bacteremia (53.0%), uncomplicated right-sided endocarditis (3.5%), complicated right-sided endocarditis (10.4%), or left-sided endocarditis (7.8%). Patients infected with MRSA had a higher success rate with daptomycin vs standard therapy, though this was not a statistically significant difference (44.4 vs 31.8%; *P*=0.28). Patients infected with MSSA had greater success with standard therapy (48.6%) than daptomycin (44.6%), which was also not statistically significant (*P*=0.76). Nine patients in each group had a final diagnosis of left-sided endocarditis; one patient in the daptomycin group and two patients in the standard therapy group had a successful outcome; Therapy failed in all patients with left-sided endocarditis caused by MRSA. Overall rates of failure were similar between groups; however, the reasons for failure differed. Daptomycin failure was more often due to relapsing *S aureus* infection (19 daptomycin vs 11 standard therapy; *P*=0.17), whereas failure with standard therapy was often related to adverse events leading to discontinuation (17 standard therapy vs eight daptomycin; *P*=0.06). Renal dysfunction was noted in 11.0% of patients in the daptomycin group and 26.3% in the standard therapy group (*P*=0.004). Secondary: Not reported
Heldman et al[8] Vancomycin 1 g IV every 12 hours or	OL, PRO, RCT Injection drug users with febrile illness	N=573 injection drug users of which 85 had	Primary: Cure rate (defined with three levels of certainty: sterile	Primary: There was no statistically significant difference in cure rates (95% with PO therapy, 88% with IV therapy; *P*=0.6); Information from subjects who did not complete the full 28 day course of treatment showed similar cure rates

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
oxacillin 2 g IV every 4 hours + gentamicin (for first 5 days) vs ciprofloxacin 750 mg PO BID and rifampin 300 mg PO BID Cefazolin was allowed when there was a contraindication to vancomycin.	meeting criteria for right-sided staphylococcal endocarditis	documented right-sided staphylococcal endocarditis Treatment: 28 days Follow-up: 35 days post completion of therapy	blood cultures six and seven days post cessation of treatment; sterile blood cultures 35 days post antibiotic withdrawal; afebrile 24 hours before hospital discharge after receiving ≥14 days of therapy), treatment failure (development of any of the following: left-sided endocarditis, heart-block, chronic heart failure, respiratory failure, hypotension, sustained/recurrent bacteremia, metastatic infection, or death) Secondary: Not reported	(90% with PO and 91% with IV; *P*=0.9) Treatment failures were reported in three patients in the parenteral therapy group and one patient in the oral therapy group. Subjects with right-sided endocarditis were predominantly male and African-American. Human immunodeficiency virus was present in 68.5% of those with suspected or confirmed right-sided staphylococcal endocarditis. Toxicity was more common with IV therapy vs PO therapy (noted in one patient receiving PO [2.8%] vs 24 patients receiving IV [61.5%]; *P*=0.0007). Nephrotoxicity occurred in 10 patients in the IV arm, vs none in the PO arm (25.6%; *P*=0.001). Secondary: Not reported
Fortun et al[9] Vancomycin 500 mg IV every 6 hours vs teicoplanin* 12 mg/kg IV every 24 hours	OL, PRO, RCT Parenteral drug users with fever, MSSA, and either septic pulmonary embolism, tricuspid regurgitation murmur or echocardiographic	N=31 30 months	Primary: Cure (microbiological eradication and satisfactory clinical response), clinical failure (no response or worsening during treatment) microbiological failure (positive blood	Primary: All patients (11/11 [100%]) in the cloxacillin group had a clinical cure compared to 6/10 (60%) in the vancomycin group and 7/10 (70%) in the teicoplanin group; *P*=0.03. Clinical failure occurred in 30% of the vancomycin group, 10% of the teicoplanin group, and none of the cloxacillin group. No patient experienced microbiological failure.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cloxacillin 2 g IV every 4 hours All 3 groups received gentamicin 1.5 mg/kg IV every 8 hours.	evidence of endocarditis		culture after day five of therapy), microbiological relapse (positive blood culture result after treatment cessation) Secondary: Not reported	Microbiological relapse occurred in 10% of the vancomycin group, 20% of the teicoplanin group, and no relapse occurred in the cloxacillin group. Adverse effects occurred in 20% of the vancomycin group, 30% of the teicoplanin group, and none of the cloxacillin group. Secondary: Not reported
Skin and Skin Structure Infections				
Arbeit et al[10] Daptomycin 4 mg/kg IV once daily vs penicillinase-resistant penicillins, including cloxacillin, nafcillin, oxacillin, or flucloxacillin*, 4 to12 g IV once daily in equally divided doses vs vancomycin 1 g IV every 12 hours	Pooled results of 2 MC, RCT Patients 18 to 85 years of age with complicated skin and skin structure infections (i.e., wound infections, major abscesses, diabetic ulcers of lower extremity, or other infected ulcers) due to gram-positive organisms requiring hospitalization and parenteral therapy for ≥96 hours	N=902 Treatment: 7 to14 days Follow-up: 20 to 28 days after therapy completion	Primary: Clinical success (resolution of signs and symptoms where no further antibiotic therapy was required), relapse or new infection, or failure (if had an inadequate response) Secondary: Not reported	Primary: Clinical success rate was 83.4% in the daptomycin group and 84.2% in the comparator groups (95% CI for the difference, -4.0 to 5.6). The response rates were comparable across baseline diagnoses. At the poststudy visit, relapse or recurrence was noted in 4.2% (15/355) of patients treated with daptomycin and 5.5% (20/367) of patients that received a penicillinase-resistant penicillins or vancomycin (95% CI for the difference, -4.4 to 1.9). Frequency of adverse events and treatment discontinuations due to any adverse event were similar in both groups (*P* value not reported). A change to oral medication was permitted if deemed appropriate. For patients with successful outcomes receiving IV treatment alone, 63% in the daptomycin group and 33% in the comparator groups required four to seven days of therapy (*P*<0.0001). Secondary: Not reported
Dodds et al[11] Linezolid 600 mg PO or IV BID or 10 mg/kg PO	MA Hospitalized patients with skin	N=813 7 to 28 days	Primary: Clinical cure and microbiological cure	Primary: There was no significant difference in clinical cure between linezolid and vancomycin treated patients (RR, 0.34; 95% CI, 0.04 to 2.89; *P*=0.32); however, there was substantial heterogeneity between the studies

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
or IV every 8 hours vs vancomycin 1 g IV every 12 hours or 10 to 15 mg/kg every 6 to 25 hours	and soft tissue infections due to hospital-acquired MRSA		Secondary: Not reported	analyzed. There was no significant difference in microbiological cure between linezolid and vancomycin (RR, 0.55; 95% CI, 0.30 to 1.01; *P*=0.05). Secondary: Not reported
Li et al[12] Linezolid 600 mg IV or PO BID vs vancomycin 1 g IV BID	MC, OL, RCT Patients with complicated skin and soft tissue infections as the primary site of MRSA infection	N=144 Treatment: ≤4weeks Observation: ≤4weeks	Primary: Length of hospital stay Secondary: Not reported	Primary: In the clinically evaluable population, the unadjusted mean length of hospital stay was 5.3 days shorter with linezolid vs vancomycin (15.7 vs 21.0 days, respectively; *P*=0.0025). After adjusting for baseline variables, the between-treatment difference in mean length of hospital stay increased to 6.5 days with linezolid vs vancomycin (14.3 vs 20.8 days, respectively; *P*<0.001). Mean duration of IV therapy was shorter in the linezolid group (5.8 vs 12.6 days; *P*<0.0001). Clinically evaluable patients had to be treated for ≥7 days, which may have extended the length of hospital stay for patients receiving vancomycin IV as compared to the linezolid group that had the option to switch to PO therapy. Secondary: Not reported
Itani et al[13] Linezolid 600 mg IV or PO every 12 hours vs vancomycin 1 g IV every 12 hours	MC, OL, RCT Hospitalized patients with complicated skin and soft tissue infections due to MRSA	N=1,200 7 days	Primary: Length of stay, duration of IV treatment, and hospital discharge rates Secondary: Not reported	Primary: Linezolid was associated with a shorter length of stay (*P*<0.01), decreased duration of IV antibiotic therapy (*P*<0.0001), and higher rates of hospital discharge (*P*<0.05) as compared to vancomycin. Secondary: Not reported
Pneumonia				

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fagon et al[14] Vancomycin 1 g IV every 12 hours vs quinupristin/dalfopristin 7.5 mg/kg IV every 8 hours Aztreonam, imipenem, or tobramycin were added if determined clinically necessary.	MC, OL, PRO, RCT Patients ≥18 years of age developing sufficiently severe nosocomial pneumonia that required ≥5 days of parenteral antibiotics	N=171 5 to 14 days	Primary: Clinical response at test-of-cure assessment (seven to 13 days after end of treatment if cure/improvement; 13 days after end of treatment if failure) in the bacteriologically evaluable population Secondary: Clinical response for the all-treated population, and in the bacteriologically evaluable population (by-pathogen bacteriologic response, by-patient bacteriologic response)	Primary: There was a clinical response in 58.3% of patients receiving vancomycin and 56.3% of patients receiving quinupristin/dalfopristin (-2.0% difference; 95% CI, -16.8 to 12.8). Thirty-two patients died in the vancomycin group compared to 38 patients in the quinupristin/dalfopristin group (*P*=0.45). Secondary: The clinical success rate was similar between groups in the all-treated population (45.3% for vancomycin and 43.3% for quinupristin/dalfopristin (-1.9% difference; 95% CI, -13.2 to 9.3). The by-pathogen bacteriologic response was similar between treatment groups (for *S pneumoniae, S aureus*, MRSA). The by-patient bacteriologic success rate was 64.3 and 58.6% in the vancomycin and quinupristin-dalfopristin groups, respectively (-5.7% difference; 95% CI, -20.2 to 8.9). There was no statistically significant difference between groups in reported adverse events.
Kalil et al[15] Linezolid vs vancomycin or teicoplanin*	MA Patients with nosocomial pneumonia	N=2,329 ≤28 days	Primary: Clinical cure, microbiological eradication, mortality, gastrointestinal events, renal failure and thrombocytopenia Secondary: Not reported	Primary: When linezolid was compared to vancomycin or teicoplanin, there were no significant differences in clinical cure (RR, 1.01; 95% CI, 0.93 to 1.10; *P*=0.83), microbiological eradication (RR, 1.10; 95% CI, 0.98 to 1.22; *P*=0.10) and mortality (RR, 0.95; 95% CI, 0.76 to 1.18; *P*=0.63). There was also no significant difference in microbiological eradication in patients with MRSA between linezolid and vancomycin or teicoplanin (RR, 1.10; 95% CI, 0.87 to 1.38; *P*=0.44). When compared to vancomycin or teicoplanin, linezolid was associated with significantly higher gastrointestinal events (RR, 2.02; 95% CI, 1.10 to 3.70; *P*=0.02) and thrombocytopenia (RR, 1.93; 95% CI, 1.30 to 2.87; *P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				When vancomycin or teicoplanin were compared to linezolid, there was no significant increase in the risk for renal failure (RR, 0.89; 95% CI, 0.56 to 1.43; *P*=0.64). Secondary: Not reported
Walkey et al[16] Linezolid vs Glycopeptides (vancomycin or teicoplanin*)	MA Patients diagnosed with pneumonia	N=1,641 Up to 28 days	Primary: Clinical success at test of cure in clinically evaluable patients Secondary: Clinical success at test of cure in the ITT population, clinical success at end of treatment for clinically evaluable patients, microbiologic success, all-cause mortality in the ITT population, drug-related adverse events in the ITT population	Primary: There was no significant difference in clinical success at test of cure with linezolid compared to glycopeptides (RR, 1.04; 95% CI, 0.97 to 1.11; *P*=0.28). Secondary: There were no significant differences between linezolid and glycopeptides in clinical success at end of treatment (RR, 1.04; 95% CI, 0.98 to 1.11; *P* value not reported) and test of cure (RR, 1.02; 95% CI, 0.93 to 1.12; *P*=0.63). There was no significant difference in clinical success at test of cure between the two groups in patients with MRSA (RR, 1.23; 95% CI, 0.93 to 1.57; *P*=0.09) and patients without MRSA (RR, 0.95; 95% CI, 0.83 to 1.09; *P*=0.48). There was also no significant difference between linezolid and glycopeptides in mortality (RR, 0.91; 95% CI, 0.69 to 1.18; *P*=0.47), microbiologic success (RR, 1.13; 95% CI, 0.97 to 1.31; *P*=0.12) and adverse events (RR, 0.96; 95% CI, 0.86 to 1.07; *P*=0.48). Risk for thrombocytopenia (RR, 2.97; 95% CI, 0.81 to 10.94; *P*=0.10) and renal impairment (RR, 1.09; 95% CI, 0.35 to 3.38; *P*=0.89) were not significantly different between the two groups.
All infections				
Falagas et al[17] Linezolid	MA Patients with complicated skin	N=6,093 Up to 28 days	Primary: Treatment success, all-cause mortality and adverse effects	Primary: For all infections, linezolid had significantly higher treatment success with the ITT patients (OR, 1.23; 95% CI, 1.06 to 1.42; *P* value not reported) and clinically assessed patients (OR, 1.41; 95% CI, 1.11 to 1.81; *P*=0.006)

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vs glycopeptides (vancomycin and teicoplanin*) or β-lactams (amoxicillin/clavulanate, ampicillin/sulbactam, cefadroxil, ceftriaxone, oxacillin, dicloxacillin)	and soft tissue infections, Gram-positive infections, uncomplicated skin and soft tissue infections, nosocomial pneumonia, community-acquired pneumonia or MRSA infections		Secondary: Treatment duration, microbiological assessment and eradication of Gram-positive cocci	compared to the glycopeptides or β-lactams. When only the blinded RCTs were analyzed, there was no significant difference between the treatments in the ITT patients (OR, 1.14; 95% CI, 0.95 to 1.38; *P* value not reported) and in clinically assessed patients (OR, 1.15; 95% CI, 0.89 to 1.48; *P*=0.29). Additionally, there was no significant difference in treatment success in the clinically assessed patients when linezolid was compared to vancomycin alone (OR, 1.44; 95% CI, 0.90 to 2.30) or β-lactams (OR, 11.34; 95% CI, 0.99 to 1.81). For the skin and soft tissue infections in the clinically assessed patients, linezolid had significantly higher treatment success compared to glycopeptides or β-lactams (OR, 1.67; 95% CI, 1.31 to 2.12; *P*<0.0001). For bacteremia in the clinically assessed patients, linezolid had significantly higher treatment success compared to glycopeptides or β-lactams (OR, 2.07; 95% CI, 1.13 to 3.78; *P*=0.02). There was no significant difference between linezolid and glycopeptides or β-lactams for the treatment of pneumonia in the clinically assessed patients (OR, 1.03; 95% CI, 0.75 to 1.42; *P*=0.84). This was similar for the subset of patients with nosocomial pneumonia (OR, 1.05; 95% CI, 0.75 to 1.46; *P* value not reported). There was no significant difference in mortality between linezolid and glycopeptides or β-lactams in the ITT patients (OR, 0.97; 95% CI, 0.79 to 1.19; *P* value not reported). There were more adverse events with linezolid compared to glycopeptides or β-lactams in the ITT patients; although, the difference was not significant (OR, 1.40; 95% CI, 0.95 to 2.06; *P*=0.09). Linezolid was associated with significantly more thrombocytopenia in the ITT patients compared to glycopeptides or β-lactams (OR, 11.75; 95% CI, 3.66 to 37.57; *P*<0.0001). Secondary: For all Gram-positive infections in the microbiologically assessed patients,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				linezolid had significantly higher treatment success compared to glycopeptides or β-lactams (OR, 1.34; 95% CI, 1.05 to 1.72; *P*=0.02). Linezolid was associated with higher rates eradication rates for *S aureus* in the microbiologically assessed patients compared to the other antibiotics (OR, 1.81; 95% CI, 1.40 to 2.34; *P*<0.00001). There was no significant differences in eradication rate for MRSA between linezolid and the other antibiotics (OR, 1.69; 95% CI, 0.84 to 3.41; *P*=0.014). There was also no significant difference between linezolid and vancomycin in patients with MRSA pneumonia (OR, 1.26; 95% CI, 0.54 to 2.96; *P* value not reported). There was no significant difference in eradication of enterococci species between linezolid and the other antibiotics (OR, 0.95; 95% CI, 0.33 to 2.73; *P*=0.93).
Shorr et al[18] Vancomycin 1 g IV every 12 hours vs linezolid 600 mg IV every 12 hours	MA (PRO, RCT) Patients with *S aureus* bacteremia (pneumonia 48 hours after hospital admission, complicated skin and soft tissue infections, or MRSA infections)	N=144 7 to 35 days	Primary: Clinical cure of primary infection at end of therapy, microbiological eradication of *S aureus* bacteremia, and overall survival Secondary: Not reported	Primary: In clinically evaluable patients, incidence of cure was 55% (28/51) in patients given linezolid and 52% (25/48) in patients given vancomycin (OR, 1.12; 95% CI, 0.51 to 2.47). In the ITT population, clinical cure occurred in 28/74 (38%) patients given linezolid and 25/70 (36%) patients given vancomycin. In patients with MRSA bacteremia, 56% (14/25) of linezolid-treated patients and 46% (13/28) of vancomycin treated patients had a cure (OR, 1.47; 95% CI, 0.50 to 4.34). Microbiological success occurred in 69% of linezolid-treated patients and 73% of vancomycin-treated patients (OR, 0.83; 95% CI, 0.37 to 1.87). The survival rate was similar for both treatment groups in patients with MRSA bacteremia as well as overall *S aureus* bacteremia. Mean duration of therapy was shorter with IV linezolid than with vancomycin (8.6 vs 11.7 days; *P*=0.004).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Linezolid was given IV >7 days after which it could be switched to PO. Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily,QID=four times daily
Study abbreviations: CI=confidence interval, DB=double-blind, ITT=intention to treat, IV=intravenous, MA=meta-analysis, MC=multicenter, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PO=oral, PRO=prospective, RCT=randomized controlled trial, RR=relative risk
Miscellaneous abbreviations: MSRA= methicillin-resistant Staphylococcus aureus, MSSA= methicillin-susceptible S aureus

Special Populations

Table 6. Special Populations[1,2]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Vancomycin	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	Renal dose adjustment is required.	Not studied in hepatic dysfunction.	B	Unknown

Adverse Drug Events

Table 7. Adverse Drug Events[2]

Adverse Event (%)	Vancomycin
Abnormal kidney function	✔
Anaphylaxis	✔
Chills	✔
Dizziness/vertigo	✔
Dyspnea	✔
Eosinophilia	✔
Fever	✔
Hearing loss	✔
Hypotension	✔
Increased blood urea nitrogen	✔
Increased serum creatinine	✔
Kidney failure	✔
Nausea	✔
Neutropenia	✔
Pain and muscle spasm	✔
Pruritus	✔
Rash	✔
Redman Syndrome	✔
Stevens-Johnson syndrome	✔
Tinnitus	✔
Thrombocytopenia	✔
Urticaria	✔
Vasculitis	✔
Wheezing	✔

✔ Percent not specified.

Contraindications/Precautions

Vancomycin is contraindicated in patients with a hypersensitivity to it. Clinically significant serum concentrations have been reported in some patients that have taken multiple oral doses, and monitoring of serum concentrations may be appropriate in some instances (e.g., patients with renal insufficiency and/or colitis). In addition, some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption and be at risk for adverse events associated with the intravenous formulation of vancomycin. The risk may be exacerbated by renal impairment.[2] Ototoxicity and nephrotoxicity are the most serious adverse events of parenteral vancomycin therapy. Ototoxicity has been reported in patients with underlying hearing loss, receiving concomitant therapy with another ototoxic agent (e.g., an aminoglycoside), and/or receiving an excessive intravenous vancomycin dose.[1]

Vancomycin should be used with caution and monitored regularly in patients with renal insufficiency, due to a greater risk of toxicity when blood concentration levels are high.[2]

Drug Interactions

Table 8. Drug Interactions[19,20]

Drug(s)	Interaction	Mechanism
Vancomycin	Aminoglycosides	Concurrent use may cause additive ototoxicity and nephrotoxicity.
Vancomycin	Nondepolarizing muscle relaxants (atracurium, gallamine triethiodide, metocurine iodide, pancuronium, pipecuronium, tubocurarine, vecuronium)	Neuromuscular blockage may be enhanced. The combination should be avoided if possible. When necessary, neuromuscular function should be monitored closely, dose of nondepolarizing muscle relaxants should be titrated; mechanical respiratory support may be needed.

Dosage and Administration

Table 9. Dosing and Administration[2]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Vancomycin	Antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile;* enterocolitis caused by *Staphylococcus aureus* (methicillin- susceptible and -resistant strains): 500 mg to 2 g in three or four divided doses for seven to 10 days	Antibiotic-associated pseudomembranous colitis antibiotic associated caused by *C difficile;* enterocolitis caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains): 40 mg/kg in three or four divided doses for seven to 10 days (maximum total daily dose should not exceed 2 g) Safety and efficacy in children have not been established.	Capsule: 125 mg 250 mg

Clinical Guidelines

The clinical guidelines contained in Table 9 are summarized globally and are not limited to the role of the vancomycin.

Table 10. Clinical Guidelines

Clinical Guideline	Recommendation(s)
Infectious Society of America/Society for Healthcare Epidemiology of America: **Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update (2010)[6]**	• Oral metronidazole is the drug of choice for the initial episode of mild to moderate *Clostridium difficile* infection. • Oral vancomycin is the drug of choice for the initial episode of severe *C difficile* infection. • For the treatment of severe complicated *C difficile* infection, oral vancomycin (and per rectum if ileus is present) with or without intravenous metronidazole is the regimen of choice. • Treatment of first recurrence of *C difficile* infection is usually the same regimen as for the initial episode. • Metronidazole should not be used beyond the first recurrence or for long-term chronic therapy due to the potential for cumulative neurotoxicity. • Treatment of the second or later recurrence of *C difficile* infection with vancomycin as a tapered and/or pulse regimen is the preferred strategy. • There are no recommendations for prevention of recurrent *C difficile* infection in patients who require continued antimicrobial therapy.

Clinical Guideline	Recommendation(s)
American Heart Association: **Prevention of Infectious Endocarditis (2007)**[21]	• Antibiotic prophylaxis is recommended for patients at the highest risk of adverse outcome from endocarditis, including those with: o Prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Previous infective endocarditis. o Congenital heart disease: ▪ Unrepaired cyanotic congenital heart disease including palliative shunts and conduits. ▪ Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure. ▪ Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization). o Cardiac transplantation recipients who develop cardiac valvulopathy. • Antibiotic prophylaxis is no longer recommended based solely on an increased lifetime risk of developing infectious endocarditis. • Antibiotic prophylaxis should be administered as a single dose before the procedure. • Prophylaxis is recommended for all patients described above who are undergoing a dental procedure which involves manipulation of the gingival tissue or the periapical region of the teeth or perforation of the oral mucosa. • Recommended regimens include: o Oral: amoxicillin 2 g (adults) or 50 mg/kg (children). o Unable to take oral medication: ampicillin or ceftriaxone or cefazolin. o Allergic to penicillins or ampicillin, oral: cephalexin or clindamycin or azithromycin or clarithromycin. • Allergic to penicillins or ampicillin and unable to take oral medications: cefazolin or ceftriaxone or clindamycin. • Antibiotic prophylaxis with a regimen described above for patients described above is recommended prior to an invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa such as tonsillectomy and adenoidectomy. • For patients described above who undergo an invasive respiratory tract procedure to treat an established infection it is recommended that the regimen contain an agent effective against *Streptococcus viridans*. If the infections is known or suspected to be caused by *Staphylococcus aureus* the regimen should include an antistaphylococcal penicillin or cephalosporin or vancomycin in patients who can't tolerate a penicillin. Vancomycin is also recommended if the infection is known or suspected to be caused by methicillin-resistant *S aureus* (MRSA). • The administration of prophylactic antibiotics is no longer recommended solely to prevent endocarditis in patients undergoing a genitourinary or gastrointestinal tract procedure. • Patients described above with infections of the genitourinary or gastrointestinal tract or for those receiving antibiotic therapy to prevent wound infection or sepsis associated with a gastrointestinal or genitourinary tract procedure, the regimen should include an agent

Clinical Guideline	Recommendation(s)
	active against enterococci, such as penicillin, ampicillin, piperacillin or vancomycin. • For patients described above scheduled for an elective cytoscopy or other urinary tract manipulation who have an enterococcal urinary tract infection or colonization, antibiotic therapy to eradicate enterococci from the urine before the procedure is reasonable. If the procedure is not elective, empiric or specific antimicrobial therapy may be administered to the patient containing an agent active against enterococci. • Amoxicillin or ampicillin is preferred for enterococcal coverage in these patients. Vancomycin may be used in patients unable to tolerate penicillin. • In patients described above who undergo a surgical procedure involving infected skin, skin structure or musculoskeletal tissue, it is reasonable that the therapeutic regimen for the treatment of the infection contain an agent active against staphylococci and β-hemolytic streptococci such as an antistaphylococcal penicillin or a cephalosporin. Vancomycin and clindamycin are options in patients unable to tolerate a β-lactam or who are known or suspected to have an infection caused by a methicillin-resistant staphylococcus.
Infectious Diseases Society of America/ American Thoracic Society: **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**[22]	<u>General recommendations</u> • Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogens(s) and knowledge of local susceptibility patterns. • Once the etiology of community acquired pneumonia has been identified via microbiological testing, antimicrobial therapy should be directed at that pathogen. <u>Empiric therapy - outpatient treatment</u> • For previously healthy patients with no risk factors for drug resistant *Streptococcus pneumoniae* infection, a macrolide (azithromycin, clarithromycin, or erythromycin) can be used. Doxycycline may also be an alternate option. • A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) is the treatment option in regions with a high rate of macrolide-resistant *S pneumoniae*, or for patients with comorbidities, such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressive conditions or use of immunosuppressive drugs. Fluoroquinolones may also be used for patients who have used antimicrobials within the previous three months. Other preferred options for these patients would be the combination of a β-lactam (ceftriaxone, cefpodoxime, or cefuroxime) plus a macrolide or doxycycline, or amoxicillin/clavulanate. <u>Empiric therapy - inpatient, non-intensive care unit treatment</u> • A respiratory fluoroquinolone or a combination of a β-lactam plus a macrolide is recommended. • Preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem may also be used for selected patients. • A respiratory fluoroquinolone should be used for penicillin allergic patients. <u>Empiric therapy - inpatient, intensive care unit treatment</u> • A β-lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either

Clinical Guideline	Recommendation(s)
	azithromycin or a respiratory fluoroquinolone. • For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended. • For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin/tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin. • The antipneumococcal, antipseudomonal β-lactams listed above can also be used with either an aminoglycoside and azithromycin, or an aminoglycoside and an antipneumococcal fluoroquinolone. • For penicillin-allergic patients, substitute aztreonam for the above β-lactam for *Pseudomonas* infection. <u>Pathogen-directed therapy</u> • *S pneumonia* (penicillin non-resistant)- penicillin G or amoxicillin preferred; alternative agents include macrolides, cephalosporins (oral cefpodoxime, cefprozil, cefuroxime, cefdinir, cefditoren or parenteral cefuroxime, ceftriaxone or cefotaxime), clindamycin, doxycycline or a respiratory fluoroquinolone. • *S pneumonia* (penicillin resistant)- agents chosen based on susceptibility; alternative agents include vancomycin, linezolid and high-dose amoxicillin (3 g/day). • *Haemophilus influenza* (non-β-lactamase producing)- amoxicillin preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. • *H influenza* (β-lactamase producing)- second- or third-generation cephalosporin or amoxicillin/clavulanate preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. • *Mycoplasma pneumonia/Chlamydia pneumonia*- macrolide, tetracycline preferred; alternative agent is fluoroquinolone. • *Legionella* species- fluoroquinolone, azithromycin preferred; alternative agent is doxycycline. • *Chlamydia psittaci*- tetracycline preferred; alternative agent is a macrolide. • *Coxiella burnetii*- tetracycline preferred; alternative agent is a macrolide. • *Francisella tularensis*- doxycycline preferred; alternative agents include gentamicin or streptomycin. • *Yersinia pestis*- streptomycin, gentamicin; recommended alternative agents include doxycycline or fluoroquinolone. • *Bacillus anthracis* (inhalation)- ciprofloxacin, levofloxacin, doxycycline preferred (usually with a second agent); alternative agents include other fluoroquinolones, rifampin, clindamycin, chloramphenicol, or a β-lactam if susceptible. • *Enterobacteriaceae*- third generation cephalosporin, carbapenem; alternative agents include a β-lactam/β-lactamase inhibitor or a fluoroquinolone. • *Pseudomonas aeruginosa*- antipseudomonal β-lactam plus ciprofloxacin or levofloxacin or aminoglycoside preferred; alternative agents include aminoglycoside plus ciprofloxacin or levofloxacin. • *Burkholderia pseudomallei*- carbapenem, ceftazidime preferred; alternative agents include fluoroquinolone or sulfamethoxazole/trimethoprim (SMX/TMP). • *Acinetobacter* species- carbapenem preferred; alternative agents include cephalosporin and aminoglycoside, ampicillin/sulbactam, colistin.

Clinical Guideline	Recommendation(s)
	• *S aureus* (methicillin susceptible)- antistaphylococcal penicillin preferred; alternative agents include cefazolin and clindamycin. • *S aureus* (methicillin resistant)- vancomycin or linezolid preferred; alternative agent is SMX/TMP. • *Bordetella pertussis*- macrolide preferred; alternative agent is SMX/TMP. • Anaerobe (aspiration)- β-lactam/β-lactamase inhibitor or clindamycin preferred; alternative agent is carbapenem. • Influenza virus- oseltamivir or zanamivir preferred. • *Mycobacterium tuberculosis*- isoniazid plus rifampin plus ethambutol plus pyrazinamide preferred. • *Coccidioides* species- no therapy generally recommended in normal host for uncomplicated infection; if therapy desired, itraconazole or fluconazole preferred; alternative agent is amphotericin B. • *Histoplasmosis*- itraconazole preferred; alternative agent is amphotericin B. • *Blastomycosis*- itraconazole preferred; alternative agent is amphotericin B. • Suspected H1N1 pandemic influenza should be treated with oseltamivir and antibacterial agents targeting *S pneumonia* and *S aureus.*
American College of Chest Physicians: **Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement (2005)**[23]	• The oral route for medications is recommended if the patient can tolerate it, and if the availability and activity of the agents are adequate. • Severity of illness, patient age, comorbidities, concomitant medications, and ease of administration are all factors that can impact the empiric treatment decision. • The use of a macrolide, doxycycline, or fluoroquinolone antibacterial agent is recommended by both the Infectious Disease Society of America and the American Thoracic Society consensus guidelines as appropriate empiric outpatient treatment for low-risk patients. • Amoxicillin/clavulanate and some second generation cephalosporins (cefuroxime, cefpodoxime, or cefprozil) are alternatives for low-risk patients. • A patient who is at high risk either because of complicated comorbidities or extensive prior antibiotic use may be a candidate for treatment with a β-lactam/macrolide combination or an antipneumococcal fluoroquinolone. • Double therapy with either a β-lactam/macrolide combination or a β-lactam/antipneumococcal fluoroquinolone should be considered in patients who would normally be considered for intensive care unit admission but have chosen to remain in the home.
Infectious Diseases Society of America/ American Thoracic Society: **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2004)**[24]	• Empiric therapy for hospital-acquired pneumonia, ventilator-associated pneumonia and healthcare-associated pneumonia should include agents from a different class than the patient has recently received. • Judicious use of combination therapy in hospital-acquired pneumonia for a specific pathogen is recommended with consideration of short-duration (five days) aminoglycoside therapy when used in combination with β-lactam to treat *P aeruginosa* pneumonia. • De-escalation of antibiotics should be considered once results are available of lower respiratory tract cultures and patient's clinical response. • For patients with uncomplicated hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia who have received initially appropriate therapy and have had a good clinical response with no evidence of infection with nonfermenting gram-

Clinical Guideline	Recommendation(s)
	negative bacilli, a shorter duration of antibiotic therapy (seven to eight days) is recommended. • The following initial empiric therapy is recommended for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with early onset of disease, no known risk factors for multidrug-resistant pathogens and any disease severity: ceftriaxone, levofloxacin, moxifloxacin, ciprofloxacin, ampicillin/sulbactam or ertapenem. • The following initial empiric therapy is recommended for hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia in patients with late onset of disease or known risk factors for multidrug-resistant pathogens and all disease severity: antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam/ β-lactamase inhibitor (piperacillin/tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin or tobramycin) plus linezolid or vancomycin.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Bacterial Meningitis (2004)**[25]	<u>Antimicrobial therapy based on the presumptive pathogen identified by positive Gram stain</u> • *S pneumonia* - vancomycin plus third-generation cephalosporin; alternative agents are meropenem or a fluoroquinolone. • *Neisseria meningitides* - third generation cephalosporin; alternative agents include penicillin G, ampicillin, chloramphenicol, fluoroquinolones, or aztreonam. • *Listeria monocytogenes* and *Streptococcus agalactiae* - ampicillin or penicillin G; alternative agents include SMX/TMP or meropenem (for *L monocytogenes*) and a third generation cephalosporin (for *S agalactiae*). • *H influenza* - third generation cephalosporin; alterative agents include chloramphenicol, cefepime, meropenem, or a fluoroquinolone. • *Escherichia coli* - third generation cephalosporin; alternative agents include cefepime, meropenem, aztreonam, fluoroquinolone, or SMX/TMP. <u>Empiric therapy based on age and predisposing condition</u> • Age <one month, *S agalactiae, E coli, L monocytogenes, Klebsiella* species: ampicillin plus cefotaxime or ampicillin plus aminoglycoside. • Age one to 23 months, *S pneumoniae, N meningitides, S agalactiae, H influenza, E coli*: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime). • Age two to 50 years, *N meningitides, S pneumoniae*: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime). • Age >50 years, *S pneumoniae, N meningitides, L monocytogenes, aerobic gram-negative bacilli*: vancomycin plus ampicillin plus third generation cephalosporin (ceftriaxone or cefotaxime). • Basilar skull fracture, *S pneumoniae, H influenza*, group A β-hemolytic streptococci: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime). • Penetrating head trauma, *S aureus*, coagulase-negative staphylococci, aerobic gram-negative bacilli: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem. • Post-neurosurgery, aerobic gram-negative bacilli, *S aureus*, coagulase-negative staphylococci: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem. • Cerebrospinal fluid shunt, coagulase-negative staphylococci, *S aureus*,

Clinical Guideline	Recommendation(s)
	aerobic gram-negative bacilli, *Propionibacterium acnes*: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem. Specific antimicrobial therapy based on pathogen and susceptibility • *S pneumonia:* o Penicillin minimum inhibitory concentration (MIC) <0.1 µg/mL: penicillin G or ampicillin, alternative therapies include third generation cephalosporin (ceftriaxone or cefotaxime), chloramphenicol. o Penicillin MIC 0.1 to 1.0 µg/mL: third generation cephalosporin (ceftriaxone or cefotaxime), alternative agents include cefepime, meropenem. o Penicillin MIC ≥2 µg/mL: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime, consider addition of rifampin if MIC of ceftriaxone is >2µg/mL), alternative agent is fluoroquinolone (gatifloxacin or moxifloxacin). o Cefotaxime or ceftriaxone MIC ≥1 µg/mL: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime, consider addition of rifampin if MIC of ceftriaxone is >2 µg/mL), alternative agent is fluoroquinolone (gatifloxacin or moxifloxacin). • *N meningitides:* o Penicillin MIC <0.1 µg/mL: penicillin G or ampicillin, alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime), chloramphenicol. o Penicillin MIC 0.1 to 1.0 µ/mL: third generation cephalosporin (ceftriaxone or cefotaxime), alternative agents include chloramphenicol, fluoroquinolone, meropenem. • *L monocytogenes*: ampicillin or penicillin G (addition of aminoglycoside should be considered), alternative agents include SMX/TMP, meropenem. • *S agalactiae*: ampicillin or penicillin G (addition of aminoglycoside should be considered), alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime). • *E coli* or *Enterobacteriaceae:* third generation cephalosporin, alternative agents include aztreonam, fluoroquinolone, meropenem, SMX/TMP, ampicillin. • *P aeruginosa:* cefepime or ceftazidime (addition of aminoglycoside should be considered), alternative agents include aztreonam, ciprofloxacin, meropenem (addition of aminoglycoside should be considered). • *H influenza:* o β-lactamase negative: ampicillin, alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime), cefepime, chloramphenicol, fluoroquinolone. o β-lactamase positive: third generation cephalosporin, alternative agents include cefepime, chloramphenicol, fluoroquinolone. • *S aureus* o Methicillin susceptible: nafcillin or oxacillin, alternative agents include vancomycin, meropenem. o Methicillin resistant: vancomycin (consider addition of rifampin), alternative agents include SMX/TMP, linezolid. • *Staphylococcus epidermidis*: vancomycin (consider addition of rifampin),

Clinical Guideline	Recommendation(s)
	alternative agent is linezolid. • *Enterococcus* species: o Ampicillin susceptible: ampicillin plus gentamicin. o Ampicillin resistant: vancomycin plus gentamicin. o Ampicillin and vancomycin resistant: linezolid.
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2005)**[26]	<u>General observations</u> • Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first or second generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of MRSA strains. • In patients with severe infection or infection that has progressed while on empirical antibiotic treatment, selection of therapeutic agents should be based on results of the gram stain, culture and drug susceptibility analysis. • In the case of *S aureus*, the clinician should assume the organism is resistant due to the high prevalence of community-associated MRSA strains. Agents effective against MRSA should be used in patients who have severe infections requiring hospitalization or those who have not responded to attempts to eradicate the infection (vancomycin, linezolid, daptomycin). Step-down treatment to other agents may be possible based on susceptibility tests. • An increase in the macrolide resistance of *Streptococcus pyogenes* has been noted, while 99.5% of strains remain susceptible to clindamycin and 100% to penicillin. • Osteomyelitis typically requires treatment for four to six weeks. <u>Animal bites</u> • The decision to administer oral or intravenous antibiotic therapy is determined by the depth and severity of the wound and the time elapsed since the bite. • Appropriate first-line therapy includes oral amoxicillin/clavulanate, doxycycline, or penicillin VK plus dicloxacillin. Other options include fluoroquinolones, SMX/TMP, and cefuroxime. The patient may also require an additional agent that is active against anaerobes, such as metronidazole or clindamycin. • Intravenous options include ampicillin/sulbactam, piperacillin/tazobactam, second generation cephalosporins, and carbapenems. Second- and third-generation cephalosporins may be used but require the addition of an antianaerobic agent. <u>Animal contact</u> • Though no randomized controlled trials exist for treatment of cutaneous anthrax, most data indicate that penicillin is effective. Less evidence supports the use of tetracyclines, chloramphenicol and erythromycin. • Bioterrorism-related anthrax should be treated with a fluoroquinolone until susceptibility tests are available, as inhalation may also have occurred. • Cat scratch disease and bacillary angiomatosis may be treated with azithromycin, erythromycin or doxycycline. Other alternatives include rifampin, SMX/TMP and ciprofloxacin. • Erysipeloid cutaneous infections should be treated with penicillin or amoxicillin; cephalosporins, clindamycin and fluoroquinolones are effective alternatives.

Clinical Guideline	Recommendation(s)
	• Glanders may be treated with ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin. • Streptomycin has been the drug of choice for bubonic plague. Tetracycline and chloramphenicol are also appropriate. Fluoroquinolones are alternative agents. • Ciprofloxacin has been suggested for both treatment and prevention of plague (bubonic and pneumonic) due to biowarfare agents. • Streptomycin is considered the drug of choice for tularemia. Acutely ill patients should receive streptomycin or gentamicin. Mild to moderate disease may be treated with oral tetracycline or doxycycline. Cellulitis • Cellulitis is commonly treatable with oral antibiotics, such as dicloxacillin, cephalexin, clindamycin or erythromycin. • For severe infection, the treatment of choice is either a penicillinase-resistant semisynthetic penicillin or a first generation cephalosporin. • In patients with severe penicillin allergy, clindamycin or vancomycin is indicated. • To reduce the risk of recurrence, it is important to keep the affected area well-hydrated and to reduce edema with elevation or compression stockings. Prophylactic treatment with monthly intramuscular benzathine penicillin, oral erythromycin, or penicillin V is also an option. Erysipelas • Oral or intravenous penicillin is the first-line treatment depending on severity. • In the presence or suspicion of staphylococcal infection, a penicillinase-resistant semisynthetic penicillin or a first generation cephalosporin is indicated. Human bites • Clenched-fist injuries typically require hospitalization and intravenous ampicillin/sulbactam, cefoxitin or one of the carbapenems. • Fluoroquinolones plus clindamycin or SMX/TMP plus metronidazole can be used in patients with severe penicillin allergy. Impetigo • Penicillinase-resistant penicillins or first generation cephalosporins are the preferred agents. • Erythromycin is indicated in the presence of pyoderma, but use is limited by erythromycin-resistant strains of *S aureus* and *S pyogenes.* • Topical therapy with mupirocin is equivalent to oral systemic antibiotics. Necrotizing infections • Antimicrobial therapy (coverage against aerobes and anaerobes) should be directed at the specific pathogen and appropriate doses should be used until operative procedures are no longer needed. • The combination of ampicillin/sulbactam, clindamycin and ciprofloxacin is first-line therapy for community-acquired mixed infection. The carbapenems, or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. In cases of penicillin allergy, alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone.

Clinical Guideline	Recommendation(s)
	• Clindamycin and penicillin should be used in necrotizing fasciitis and/or streptococcal toxic shock syndrome caused by group A streptococci. The efficacy of intravenous gamma globulin in these cases is still under investigation. • *Streptococcus* infection should be treated with high-dose penicillin or ampicillin plus clindamycin. • *S aureus* infection, often associated with pyomyositis, should be treated with nafcillin, oxacillin, or cefazolin. Vancomycin should be reserved for resistant strains or can be used in cases of severe penicillin allergy, as well as linezolid, quinupristin/dalfopristin or daptomycin. Clindamycin is limited by its potential of cross-resistance. • In gas gangrene, the efficacy of hyperbaric oxygen is inconclusive. Standard antibiotic treatment is penicillin plus clindamycin. <u>Soft-tissue infections caused by community-acquired MRSA</u> • They are often susceptible to non-β-lactam antibiotics, and standard treatment includes doxycycline, clindamycin, SMX/TMP, rifampin, or fluoroquinolones, specifically levofloxacin, gatifloxacin or moxifloxacin. <u>Surgical site infections</u> • Surgical site infections often resolve without the use of antibiotics. • In patients with a temperature >38.5°C, pulse rate >100 beats/minute or erythema diameter >5 cm from incision with induration or necrosis, a short course of antibiotics is recommended. • For wounds of the perineum or operation on the gastrointestinal tract or female genital tract, cefotetan or ampicillin/sulbactam or a fluoroquinolone plus clindamycin is recommended. • For clean wounds on the trunk, head, neck or extremities, cefazolin, oxacillin or clindamycin are recommended. <u>Immunocompromised patients</u> • In neutropenic patients, empiric broad-spectrum antibacterial therapy is recommended at the first sign of infection including fever. • For gram-negative infections, monotherapy with carbapenems, cephalosporins with antipseudomonal activity, and piperacillin/tazobactam, are all appropriate. Recommended combination therapy regimens are (1) an aminoglycoside plus either an antipseudomonal penicillin or an extended-spectrum cephalosporin, or (2) an extended-spectrum penicillin plus ciprofloxacin. Adjunct treatment with granulocyte colony-stimulating factor or granulocyte-monocyte colony-stimulating factor is recommended. • For gram-positive infections, vancomycin is not recommended for empirical antibiotic therapy because of resistance; linezolid or daptomycin are appropriate alternatives to vancomycin. • For *Nocardia* infection, first-line therapy is SMX/TMP. Other sulfonamide antibiotics and imipenem are also appropriate. • Empirical antifungal therapy is a common practice in neutropenic patients with persistent fever. Amphotericin B, caspofungin and voriconazole are appropriate. • Amphotericin B and its lipid formulations have been the gold standard to treatment for yeast and fungal infections in neutropenic patients. Caspofungin and voriconazole appear to be as effective as amphotericin B and with less serious acute toxicity but are more expensive.

Clinical Guideline	Recommendation(s)
	• Treatment of non-tubercular mycobacterial infections of the skin and soft tissues requires combination therapy that should include a macrolide. • Cutaneous *Nocardia* infections should be treated with SMX/TMP, the treatment of choice. Other sulfa antibiotics and imipenem are also effective. • Initial therapy for Cryptococcal cellulitis is fluconazole, which is also used to complete therapy after patients have shown an initial response to amphotericin B and 5-flucytosine induction therapy. • Amphotericin B is recommended in patients with cellular immune deficiency and disseminated histoplasmosis. Itraconazole may replace amphotericin B after one to two weeks to complete at least six to 12 months of treatment. • Prevention of viral reactivation with oral acyclovir, famciclovir or valacyclovir is an important component of the treatment of cutaneous varicella zoster virus. • Acyclovir is the treatment of choice for herpes simplex virus infections, though famciclovir and valacyclovir are also highly effective. • Prolonged ganciclovir therapy is the treatment of choice for cutaneous cytomegalovirus.
Infectious Diseases Society of America: **Diagnosis and Treatment of Diabetic Foot Infections (2004)**[27]	• Aerobic gram-positive cocci are the usual pathogens responsible for acute infections due to breaks in the skin. The most common pathogens identified are *S aureus* and the b-hemolytic streptococci. • Chronic wounds involve more complex pathogens including enterococci, Enterobacteriaceae, anaerobes, *P aeruginosa* and non-fermentative gram-negative rods. • Antibiotics are not recommended in uninfected wounds. • Most patients with mild to moderate infections can be treated as outpatients. • For severe infections, initial empiric antibiotic therapy should include coverage for gram-positive, gram-negative and anaerobic pathogens and should be administered parenterally. • Mild to moderate infections can usually be treated with narrow-spectrum agents which cover gram-positive cocci. • On the basis of available data, no single drug or drug combination appears to be “superior” to another. • Cephalosporins have been used and include cefoxitin, ceftizoxime, ceftriaxone and cephalexin. • Osteomyelitis typically requires four to six weeks of antibiotic therapy.
Infectious Disease Society of America/ Surgical Infection Society: **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)**[28]	Community-acquired infection of mild to moderate severity in adults • Single agent therapy with ticarcillin/clavulanate, cefoxitin, ertapenem, moxifloxacin or tigecycline or combination therapy of metronidazole with cefazolin, cefuroxime, ceftriaxone, levofloxacin or ciprofloxacin is preferred over regimens with substantial antipseudomonal activity. • Ampicillin/sulbactam, cefotetan and clindamycin are not recommended due to high rates of resistance. • Empiric therapy with antifungals or coverage for *Enterococcus* is not recommended. • Aminoglycosides are not recommended for routine use because of the risk of toxicity. • Agents recommended for higher severity infections are not recommended for mild to moderate community-acquired infections because of the risk of toxicity and development of resistance.

Clinical Guideline	Recommendation(s)
	High-risk community-acquired infections in adults • The empiric use of broad-spectrum agents with activity against gram-negative organisms including meropenem, imipenem/cilastatin, doripenem, piperacillin/tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole or ceftazidime or cefepime in combination with metronidazole is recommended. • Aztreonam plus metronidazole with the addition of an agent effective against gram-positive cocci is an alternative. • Quinolones should not be used unless hospital surveys indicate >90% susceptibility of *E coli*. • In the absence of evidence of resistant pathogens, aminoglycosides or another second agent effective against gram-negative facultative and anaerobic bacilli and/or agents effective against MRSA should not be used. • Empiric used of agents effective against enterococci is recommended. Health care-associated infection in adults • Multidrug regimens that include agents with expanded spectra of activity against gram-negative facultative and anaerobic bacilli, such as meropenem, imipenem/cilastatin, doripenem, piperacillin/tazobactam or ceftazidime may be required. Therapy should be tailored based on local microbiology results and culture and susceptibility reports when they become available. Antifungal therapy • For patients with severe-community acquired or health care-associated infections with cultures that show *Candida*, antifungal therapy is recommended. • Fluconazole is an appropriate first-line choice if *C albicans* is isolated. • For fluconazole resistant *Candida* species and critically ill patients, an echinocandin (caspofungin, micafungin or anidulafungin) is recommended. • Amphotericin B is not recommended due to its toxicity. Anti-enterococcal therapy • Empiric therapy for enterococci is recommended for patients with health care-associated infections when enterococci are recovered, patients with post-operative infections, patients that have received cephalosporins or other antimicrobial agents selecting for *Enterococcus* species, immunocompromised patients and patients with valvular heart disease or prosthetic intravascular materials. • Therapy should be directed against *E faecalis* and can include ampicillin/piperacillin and vancomycin. • Empiric therapy for vancomycin-resistant *E faecium* is not recommended unless patient is at very high risk or patient is known to be colonized with *E faecium*. Anti-MRSA therapy • Empiric therapy for MRSA should be provided to patients with health care-associated infections with known colonization with MRSA or are at high risk for MRSA infection because of prior treatment failure and significant antibiotic exposure. • Vancomycin is recommended for treatment if suspected or proven

Clinical Guideline	Recommendation(s)
	infection due to MRSA. Cholecystitis and cholangitis in adults • For patients with suspected cholecystitis and cholangitis, antibiotic therapy is recommended when a biliary-enteric anastomosis is present. • In community-acquired acute cholecystitis of mild to moderate severity, cefazolin, cefuroxime or ceftriaxone is recommended. • In acute cholangitis following bilio-enteric anastomosis of any severity and community-acquired acute cholecystitis of severe physiologic disturbance, advance age or immunocompromised state, a combination regimen with metronidazole and imipenem/cilastatin, meropenem, doripenem, piperacillin/tazobactam, ciprofloxacin, levofloxacin or cefepime is recommended. • For health care-associated biliary infection of any severity, the above regimen (a combination regimen with metronidazole and imipenem/cilastatin, meropenem, doripenem, piperacillin/tazobactam, ciprofloxacin, levofloxacin or cefepime) with the addition of vancomycin is recommended. Pediatric infection • For pediatric patients with complicated intra-abdominal infections, acceptable broad-spectrum regimens include an aminoglycoside based regimen, a carbapenem (imipenem, meropenem, or ertapenem) a β-lactam/β-lactamase inhibitor combination (piperacillin/tazobactam or ticarcillin/clavulanate) or an advanced generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime or cefepime) with metronidazole. • For children with severe reactions to β-lactam antibiotics, ciprofloxacin plus metronidazole or an aminoglycoside based regimen are recommended. • In neonates with necrotizing enterocolitis, the broad-spectrum antibiotics that may be useful are ampicillin, gentamicin and metronidazole; ampicillin, cefotaxime and metronidazole; or meropenem. For suspected MRSA, vancomycin may be used in place of ampicillin. If the cultures are consistent with fungal infections, fluconazole and amphotericin should be used.
Infectious Diseases Society of America: **Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children (2011)**[29]	Empiric therapy for community-associated MRSA in skin and soft-tissue infections • For outpatients oral antibiotic options include: clindamycin, SMX/TMP, a tetracycline (doxycycline or minocycline) and linezolid. If additional coverage for β-hemolytic streptococci and community acquired-MRSA is desired, options include: clindamycin alone, SMX/TMP or tetracycline in combination with a β-lactam (e.g., amoxicillin) or linezolid alone. • For hospitalized patients with complicated skin and soft-tissue infections, therapy for MRSA in addition to broad-spectrum antibiotics should be considered depending on culture data. Options include: intravenous vancomycin, intravenous or oral linezolid, intravenous daptomycin, intravenous telavancin and intravenous or oral clindamycin. • In hospitalized children with complicated skin and soft-tissue infections that are stable without ongoing bacteremia or intravascular infection, intravenous clindamycin (if resistance rate is low) with transition to oral therapy is recommended. Oral or intravenous linezolid is an alternative therapy.

Clinical Guideline	Recommendation(s)
	Therapy for MRSA bacteremia and infective endocarditis • For adults with bacteremia and infective endocarditis with native valve, vancomycin or daptomycin is recommended. • For patients with infective endocarditis and prosthetic valve, vancomycin plus rifampin and gentamicin is recommended. • For children with bacteremia and infective endocarditis, vancomycin is recommended. Limited data shows daptomycin as a treatment option. Therapy for MRSA pneumonia • For health-care associated or community acquired pneumonia, intravenous vancomycin or oral or intravenous linezolid or oral or intravenous clindamycin, if the strain is susceptible is recommended. • For children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, intravenous clindamycin can be used if the clindamycin resistance is low with a transition to oral if the strain is susceptible. Linezolid is an alternative. Therapy for bone and joint infections • For osteomyelitis and septic arthritis, antibiotic options include intravenous vancomycin, intravenous daptomycin, intravenous or oral SMX/TMP with rifampin, intravenous or oral linezolid and intravenous or oral clindamycin. In patients with concurrent bacteremia, rifampin can be added to the previous agents after clearance of bacteremia. • For early-onset or acute hematogenous prosthetic joint infections involving a stable implant with short duration of symptoms and debridement, initiate therapy with parental therapy (see above)plus rifampin for two weeks followed by rifampin plus a fluoroquinolone, SMX/TMP, a tetracycline or clindamycin for three or six months. • For early-onset spinal implant infections or implants in an actively infected site, initial parental therapy plus rifampin followed by prolonged oral therapy is recommended. • For children with acute hematogenous MRSA osteomyelitis and septic arthritis, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, intravenous clindamycin can be used if the clindamycin resistance is low with a transition to oral if the strain is susceptible. Alternative agents include daptomycin or linezolid. Therapy for MRSA infections of the central nervous system • For meningitis, brain abscess, subdural empyema and spinal epidural abscess, intravenous vancomycin is recommended. Rifampin may be added to the regimen. Alternative agents include linezolid or SMX/TMP. • For children, intravenous vancomycin is recommended. Therapy for persistent bacteremia and vancomycin treatment failures • The following treatment regimens should be considered: high-dose daptomycin, if isolate is susceptible, in combination with another agent (e.g., gentamicin, rifampin, linezolid or a β-lactam antibiotic). • If reduced susceptibility to vancomycin and daptomycin is present, treatment options include: quinupristin/dalfopristin, SMX/TMP, linezolid, telavancin. Therapy of MRSA infections in neonates

Clinical Guideline	Recommendation(s)
	• For localized neonatal pustulosis in a premature or very low-birthweight infant or more-extensive disease involving multiple sites in a full-term infant, intravenous vancomycin or clindamycin is recommended, at least initially, until bacteremia is excluded. • For neonatal MRSA sepsis, intravenous vancomycin is recommended. Clindamycin and linezolid are alternatives for non-endovascular infections.
National Surgical Infection Prevention Project: **Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project (2004)**[30]	Sponsoring organizations include the following: American Academy of Orthopaedic Surgeons; American Association of Critical Care Nurses; American Association of Nurse Anesthetists; American College of Surgeons; American College of Osteopathic Surgeons; American Geriatrics Society; American Society of Anesthesiologists; American Society of Colon and Rectal Surgeons; American Society of Health-System Pharmacists; American Society of PeriAnesthesia Nurses; Ascension Health; Association of PeriOperative Registered Nurses; Association for Professionals in Infection Control and Epidemiology; Infectious Diseases Society of America; Medical Letter; Premier; Society for Healthcare Epidemiology of America; Society of Thoracic Surgeons; and Surgical Infection Society. <u>Cardiothoracic and vascular surgery</u> • Intravenous cefazolin or intravenous cefuroxime are recommended. • If the patient has a β-lactam allergy, intravenous vancomycin is appropriate and intravenous clindamycin is an alternative. <u>Colorectal surgery</u> • Oral neomycin plus oral erythromycin or oral neomycin plus oral metronidazole are recommended along with administration of a mechanical bowel preparation. • Intravenous cefotetan or intravenous cefoxitin are recommended for parental prophylaxis. Intravenous cefazolin plus oral metronidazole are recommended as a cost-effective alternative. • For patients with a confirmed allergy or adverse reaction to β-lactams, intravenous clindamycin plus intravenous gentamicin, intravenous aztreonam or intravenous ciprofloxacin; intravenous metronidazole plus intravenous gentamicin or intravenous ciprofloxacin are recommended. A single dose of intravenous levofloxacin can be substituted for intravenous ciprofloxacin. <u>Gynecologic and obstetric surgery</u> • Intravenous cefotetan is preferred for abdominal or vaginal hysterectomy. Intravenous cefazolin and intravenous cefoxitin are reasonable alternatives. • Intravenous metronidazole is an alternative, but may be less effective as monotherapy. • For patients with a β-lactam allergy, intravenous clindamycin plus intravenous gentamicin, intravenous aztreonam or intravenous ciprofloxacin; intravenous metronidazole plus intravenous gentamicin or intravenous ciprofloxacin; or intravenous clindamycin monotherapy are recommended. A single dose of intravenous levofloxacin can be substituted for intravenous ciprofloxacin.

Conclusions

Oral vancomycin has only been shown to be effective in the treatment of enterocolitis or *Clostridium difficile* pseudomembranous colitis. Oral vancomycin is not used for the same conditions as parenteral vancomycin, and vice-versa. Clinical trials have demonstrated the similar efficacy between vancomycin and other agents used to treat *C difficile* including metronidazole and a recently-approved macrolide antibiotic, fidaxomicin.[3-5] In addition, guidelines recommend oral vancomycin as an initial treatment of severe *C difficile* infection.[6] Oral vancomycin is not available generically.

Appendix I: Utilization Within This Drug Class for DVHA: April 1, 2011 to September 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost $	Avg $/Rx
Vancocin® (vancomycin capsule)	23	40	100.00%	$93,141.71	$2,328.54
Class Total:	**23**	**40**	**100.00%**	**$93,141.71**	**$2,328.54**

Recommendations

At this time, Vancocin® (vancomycin capsule) is not managed by the Department of Vermont Health Access (DVHA) and is available without a prior authorization (PA). In recognition of its limited indication, availability of generic alternatives, and cost considerations, it is recommended to move Vancocin® from preferred to nonpreferred status with the following PA criteria:

- The patient's diagnosis or indication is enterocolitis caused by *Staphylococcus aureus.*

OR

- The patient's diagnosis or indication is antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*

AND

- The patient has had a therapeutic failure, adverse reaction or contraindication to metronidazole.

OR

- The prescriber provides a clinically compelling rationale why metronidazole is not appropriate for the patient. (e.g. patient has severe *Clostridium difficile* infection, history of recurrent infections).

Note: IV vancomycin products are not recommended to be managed at this time.

References

1. Anti-infective agents 8:00, Antibacterials 8:12, Miscellaneous Agents 8:12.28, Glycopeptides 8:12.28.16. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2011 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2011 [cited 2011 Aug 1]. Available from: http://online.statref.com.
2. Vancocin® [package insert]. Exton (PA): ViroPharma Incorporated; October 2005.
3. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007 Aug 1;45(3):302-7.
4. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, et al. Fidaxomicin versus vancomycin for clostridium difficile infection. N Engl J Med. 2011;364:422-31.
5. Nelson R. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD004610.
6. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al.; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010 May;31(5):431-55.
7. Fowler VG, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by staphylococcus aureus. N Eng J Med. 2006;355:653-65.
8. Heldman AW, Hartert TV, Ray SC, Daoud EG, Kowalski TE, Pompili VJ, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med. 1996;101(1):68-76.
9. Fortun J, Navas E, Martinex-Beltran J, et al. Short-course therapy for right-side endocarditis due to Staphylococcus aureus in drug abusers: cloxacillin versus glycopeptides in combination with gentamicin. Clin Infect Dis. 2001;33:120-5.
10. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI; Daptomycin 98-01 and 99-01 Investigators. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis. 2004 Jun 15;38(12):1673-81.
11. Dodds TJ, Hawke CI. Linezolid versus vancomycin for MRSA skin and soft tissue infections (systematic review and meta-analysis). ANZ J Surg. 2009 Sep;79(9):629-35.
12. Li JZ, Willke RJ, Rittenhouse BE, Rybak MJ. Effect of linezolid versus vancomycin on length of hospital stay in patients with complicated skin and soft tissue infections caused by known or suspected methicillin-resistant staphylococci: results from a randomized clinical trial. Surg Infect (Larchmt). 2003 Spring;4(1):57-70.
13. Itani KM, Weigelt J, Li JZ, Duttagupta S. Linezolid reduces length of stay and duration of intravenous treatment compared to vancomycin for complicated skin and soft tissue infections due to suspected or proven methicillin-resistant Staphylococcus aureus (MRSA). Int J Antimicrob Agents. 2005 Dec;26(6):442-8.
14. Fagon JY, Patrick DW, Haas A, Nosocomial Pneumonia Group. Treatment of gram-positive nosocomial pneumonia: prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Am J Respir Crit Care Med. 2000;161:753-62.
15. Kalil AC, Murthy MH, Hermsen ED, Neto FK, Sun J, Rupp ME. Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: a systematic review and meta-analysis. Crit Care Med. 2010 Sep;38(9):1802-8.
16. Walkey AJ, O'Donnell MR, Wiener RS. Linezolid vs glycopeptide antibiotics for the treatment of suspected methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a meta-analysis of randomized controlled trials. Chest. 2011 May;139(5):1148-55.
17. Falagas ME, Siempos II, Vardakas KZ. Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomized controlled trials. Lancet Infect Dis. 2008 Jan;8(1):53-66.
18. Shorr AF, Kunkel MJ, Kollef M. Linezolid versus vancomycin for Staphylococcus aureus bacteraemia: pooled analysis of randomized studies. J Antimicrob Chemother. 2005 Nov;56(5):923-9.

19. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2011 Jul 22]. Available from: http://www.thomsonhc.com/.
20. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2011 [cited 2011 Jul 22]. Available from: http://online.factsandcomparisons.com.
21. Wilson W, Taubert K, Gewitz M, Lockhart P, Baddour L, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116:1736-54.
22. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-72.
23. Ramsdell J, Narsavage GL, Fink JB; American College of Chest Physicians' Home Care Network Working Group. Management of community-acquired pneumonia in the home: an American College of Chest Physicians clinical position statement. Chest. 2005 May;127(5):1752-63.
24. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005 Feb 15;171(4):388-416.
25. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, Whitley RJ. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004 Nov 1;39(9):1267-84.
26. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005 Nov 15;41(10):1373-406.
27. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al.; Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004 Oct 1;39(7):885-910.
28. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect (Larchmt). 2010 Feb;11(1):79-109.
29. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al.; Infectious Diseases Society of America. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011 Feb 1;52(3):e18-55.
30. Bratzler DW, Houck PM; Surgical Infection Prevention Guidelines Writers Workgroup; Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004 Jun 15;38(12):1706-15. Epub 2004 May 26.